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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,699	08/05/2003	Pablo Umana	1975.0010004/TJS	5489

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
11/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/633,699	UMANA ET AL.	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/27/07*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *109,110,112-115,118-121,125-128 and 132-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *109, 110, 112-115, 118-121, 125-128, and 132-142* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt and entry of the amendments dated 4/30/2007 and 8/27/2007 is acknowledged. After entry of the amendment, claims 109, 110, 112-115, 118-121, 125-128, and 132-142 are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 112

Claims 134, 135, and 137-139 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **These are new rejections necessitated by amendment of the claims.**

Claims 134, 135, and 137-139 depend from canceled claim 124. It is thus unclear what the metes and bounds of the claimed subject matter might be. In the interest of compact prosecution, the claims have been examined as being dependent upon claim 109 or 110.

Claim 135 recites the limitation "said altered activity" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 139 recites the limitation "said at least one glycoprotein-modifying glycosyltransferase" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim.

Claims 109, 110, 112-115, 118-121, 125-128, and 132-142 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons made of record in the Office Action dated 10/31/2006, for reasons set forth below, and because of amendment of the claims.**

Amended claims 109, 110, 118 and 133 (from which all other claims depend) recite recombinant antibodies isolated from "a Chinese hamster ovary cell" (CHO cell) that have a majority of nonfucosylated N-linked oligosaccharides, and which have increased Fc-mediated cellular cytotoxicity (or ADCC, claim 109), or increased Fc receptor binding affinity (claim 110). The claims thus encompass a broad genus of antibodies, i.e. any antibody, produced from any CHO cell, wherein the antibody has a majority of nonfucosylated N-linked oligosaccharides, and has increased ADCC. The response indicates support for the amendment may be found in previous claims 123 and 131, on pages 22-23, 37-38 of the specification, and in Fig. 9.

Claims 123 and 131 are not original claims, they were added by amendment on 12/22/2004. Thus, these claims cannot provide support for the instant claims in the manner prescribed by 35 USC 112 1st ¶ (see MPEP §2163 I B.). Second, pages 22-23 and 37-38 do not describe the claimed invention, which encompasses any recombinant antibody produced in any type of CHO cell, with a majority of nonfucosylated N-linked oligosaccharides and increased ADCC. What is described on pages 22-23, 37-38, and the remainder of the specification, are

antibodies with increased ADCC produced from CHO cells modified to express a cloned GnT III gene at various levels, and a link between the increased ADCC and increased complex N-linked oligosaccharides with bisecting GlcNAc (as previously set forth in the Office Action dated 10/31-2006). The highest levels of nonfucosylated N-linked oligosaccharides (found in the CE7-15t sample and represented by the m/z 1664 peak in Fig 9E) was not linked to increased ADCC, but rather, was linked to the opposite affect:

> "*...the highest level of [GntIII] expression actually led to reduced ADCC (Figure 12, sample CE7-15t).*"
>
> and;
>
> *"These results show that there is an optimal range of GntIII expression in CHO cells for ADCC activity, and comparison with oligosaccharide profiles shows that activity correlates with the level of Fc-associated, bisected complex oligosaccharides."* (emphasis added)
>
> See page 38, lines 21-21 and lines 24-26 of the specification.

Thus, the specification provides no link between increased proportions of nonfucosylated oligosaccharides, or a majority of nonfucosylated oligosaccharides, and ADCC. Rather, is repeatedly teaches such a link between ADCC and bisected complex oligosaccharides, many of which are fucosylated according to the results set forth in the specification (see below). Furthermore, there is no disclosure of any CHO cells, other than the CHO CE7-60t and CHO Ce7-30t expressing a heterologous GnTIII enzyme, that produce antibodies with increased ADCC. In fact, it appears that antibodies prepared from wild-type CHO cells (within the scope of cells recited in the claim) have none of the properties recited in the claim, for example,

antibodies produced in wild-type CHO cells are heavily fucosylated (Shields et al, J. Biol. Chem., 2002, of record).

Finally, the antibodies presented in the instant application that had increased ADCC did not have a "majority" of nonfucosylated oligosaccharides. Analysis of the oligosaccharide profiles of the CE7-60t and -30t antibodies reveals that a majority of the oligosaccharides are fucosylated. In Fig. 9C and D (CE7-60t and -30t, respectively), the peaks at m/z 1486, 1648, 1689, and 1851 all represent fucosylated oligosaccharides according to the disclosure (e.g. pages 37-39 and Figs 10-11), and, absent evidence to the contrary, represent a majority of the oligosaccharides: the m/z 1689 and 1851 are the two largest peaks in Fig. 9C and D. The m/z 1689 and 1851 peaks represent bisected complex oligosaccharides that are fucosylated, according to Fig. 11, the very peaks which led applicants to conclude that an increase in bisected complex oligosaccharides leads to an increase in ADCC (e.g. pages 36-39 of the specification).

Given the above, the specification cannot support such a broad claim to any recombinant antibody, produced from any CHO cell, that has a majority of nonfucosylated oligosaccharides and increased ADCC.

Response to Arguments

Applicant's arguments filed 4/30/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) applicants have previously identified support for the amended claims in the reply dated 7/18/2005, and that the Examiner has not addressed this alleged support; 2) the Examiner has misinterpreted the findings of the specification, i.e. decreased fucosylation is a necessary characteristic of the claimed antibodies because oligosaccharides first modified by the GnTIII enzyme can no longer be fucosylated by the α-1,6-

fucosyltransferase; 3) the instant disclosure inherently discloses the claimed antibodies, as supported by the rulings of *In re Papesch* and *Kennecott v. Kyocera*, and thus the inherent feature of the antibodies in the specification provides support as required by 35 USC 112 first ¶.

Regarding 1), this issue was addressed in the Office Action dated 10/31/2006, which stated that the only support found in the specification for nonfucosylated oligosaccharides is a single example of a specific antibody produced in modified CHO cells, (i.e. the CE7-15t, -30t, and -60t preparations from Example 3, column 26 of the '084 patent and beginning on page 31 of the instant specification). The nonfucosylated oligosaccharides are not disclosed as correlated with an increase in ADCC for this antibody, or for antibodies in general, for reasons set forth above. Basically, the antibodies having increased ADCC did not have a majority of nonfucosylated oligosaccharides, and the antibody that did, CE7-15t, did not have increased ADCC, rather, it had decreased ADCC. A review of the remainder of the specification, including the passages cited by applicants reveals no further support for such claims.

Regarding 2), the Examiners interpretation, set forth above and in the previous Office Action, merely repeats many of the findings discussed by applicants in the instant application. There is very little to "misinterpret": the instant application simply does not link increased ADCC (or increased Fc receptor affinity) with a decrease in fucosylation. Rather, to reiterate, the data, and applicants own interpretation of the data, links increased ADCC with an increase in bisected complex oligosaccharides, not an increase in nonfucosylated oligosaccharides. Applicants have yet to explain how the skilled artisan, upon reading the instant disclosure, could link increased ADCC with decreased fucosylation when the antibody with the least fucosylation had the least ADCC. Further, many of the oligosaccharides are clearly fucosylated according to

applicants own interpretation and figures (again, see Example 3 and Figs. 9-11), even when the antibodies are expressed in CHO cells expressing GnTIII. This is because fucosylation can occur before the action of GnTIII, as is clearly demonstrated in Figs. 10 and 11: that is, the substrates for the GnTIII enzyme are already fucosylated in these figures prior to the action of GnTIII.

Regarding 3), a review of *In re Papesch* reveals it is directed to disclosure under 35 USC 103, i.e. the sufficiency of a prior art reference to render a claim, or a claim limitation, obvious. This is an entirely different statute, with completely different requirements and considerations than the instant rejection. Furthermore, and more importantly, neither *In re Papesch* or *Kennecott v. Kyocera* provides any support or guidance regarding how applicants can claim a genus of compounds (i.e. the claimed antibodies) when not even a single species within the genus is disclosed in the patent application. For reasons set forth above, (to review, the disclosed antibodies with increased ADCC did not have a majority of nonfucosylated oligosaccharides, and the antibody with a majority of nonfucosylated oligosaccharides had decreased ADCC) there is no support, either literal or inherent, for the claimed antibodies. Thus, the claims comprise New Matter.

Claim Rejections - 35 USC § 102

Claims 109, 110, 114, 118, 133, 135, 136, and 140-142 are rejected under 35 U.S.C. 102(b) as being anticipated by Kilmartin et al (J. Cell Biol., 1982) as evidenced by Shinkawa et al (JBC, 2003). **This rejection is maintained for reasons made of record in the**

Office Action dated 10/31/2006, and for reasons set forth below. Claim 118 has been added to the rejection due to amendment of the claim.

Regarding claim 118, for reasons of record, Kilmartin et al teach a rat antitubulin monoclonal antibody produced in YB2/0 cells. As evidenced by Shinkawa et al, the YB2/0 cells express low levels of α1,6-fucosyltransferase, therefore producing antibodies having a greater proportion of nonfucosylated oligosaccharides than those produced in CHO cells. The YB2/0 cells also had an increased content of GlcNAc than the CHO-produced antibodies (page 3469, first column, second ¶), and thus an increased proportion of GlcNAc residues to fucose residues.

Response to Arguments

Applicant's arguments filed 4/30/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Kilmartin does not mention glycoengineering of antibodies; 2) the claims have been amended to recite engineered CHO cells, a limitation not taught by Kilmartin et al, which teaches YB2/0 cells.

Regarding 1) and 2), product-by-process claims are not limited to the manipulations of the recited steps. See MPEP 2113. As such, the antibody of Kilmartin et al is still considered to inherently have all of the limitations recited in the instant claims for reasons made of record. Furthermore, regarding 2), in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., engineered CHO cells) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The claims

recite glycoengineered antibodies, but do not recite engineered CHO cells, only "a Chinese hamster ovary cell", as set forth above in the USC 112 1st ¶ rejection.

Claims 109, 110, 114, 118, 125-128, 133, 135-136, 138, and 140-142 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothman et al (Mol. Immunol, 1989, cited by applicants) as evidenced by Shields et al (JBC, 2002) and Wright et al (TIBTECH, 1997, cited by applicants). **This rejection is maintained for reasons made of record in the Office Action dated 10/31/2006, and for reasons set forth below. Claim 118 has been added to the rejection due to amendment of the claim.**

Rothman et al teach the production of murine anti-tumor monoclonal antibodies (MAbs) in cells treated with a series of carbohydrate processing inhibitors such as Castanospermine (Cs), N-methyldeoxy-nojirimycin (MdNM), deoxymannojirimycin (DMM), monensin (Mon), and swainsonine (Sw). The modified oligosaccharides of the MAbs were characterized as lacking fucosylation, which is considered to yield an oligosaccharide with an increased proportion of GlcNAc residues (inherently present in all N-linked oligosaccharides, e.g. Fig. 2 of Shinkawa et al) to fucose residues relative to antibodies prepared in the absence of the processing inhibitors.

Response to Arguments

Applicant's arguments filed 4/30/2007 have been fully considered but they are not persuasive. Applicants essentially assert that: 1) Rothman et al fail to teach a glycoengineered antibody produced by a CHO cell.

Regarding 1) product-by-process claims are not limited to the manipulations of the recited steps. See MPEP 2113. As such, the antibodies of Rothman et al are still considered to inherently have all of the limitations recited in the instant claims for reasons made of record.

Double Patenting

Claims 109, 110, 120, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 113-116 and 256-258 of copending Application No. 10/981,738.

Claims 109, 110, 114, 115, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 96-98, 108-111, 213, 261-263, and 273-276 and 256-258 of copending Application No. 10/761,435.

Claims 109, 114, 115, 128, and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 74-85 of copending Application No. 10/633, 697.

Claims 109 and 133 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 127 of copending Application No. 10/437,388. **The above rejections are maintained for reasons made of record in the previous Office Action and for reasons set forth below.**

Response to Arguments

Applicant's arguments filed 4/30/2007 have been fully considered but they are not persuasive. Applicants request these provisional rejections be held in abeyance until indication

of allowable subject matter. Since no terminal disclaimer has been filed, the rejections are maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633

/Joseph Woitach/
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